

REMARKS

I. Status of the Claims

Reconsideration of the present application is respectfully requested. Claim 1 has been amended to incorporate the Markush group of claims 11-14 to more particularly claim a specific embodiment of the claimed invention. This amendment is fully supported by the original claims as filed. Claims 11-14 are currently canceled without prejudice. Claims 5-6, 17, 18, 32 and 38 have been previously canceled without prejudice. Therefore, Claims 1-4, 7-10, 15-16, 19-31, 33-37 and 39 are currently pending. No new matter has been added by way of this amendment.

II. Rejections Under 35 U.S.C. §103(a)

Claims 1-4, 7-16, 19-31, 33-37, and 39 stand rejected under 35 U.S.C. 103(a) as obvious over U.S. Patent No. 5,688,516 (to Raad et al.) in view of Domenico et al. (*Journal of Antimicrobial Chemotherapy*, 28(6):801-810,1991), International Publication No. WO 97/25085 (to Modak et al.), and U.S. Patent No. 6,719,991 (to Darouiche et al.). The Examiner maintains that Raad describes a combination of antimicrobials (e.g., minocycline), and chelators (e.g., zinc citrate, citrate and bismuth), which are effective antimicrobials against Staphylococci and Candida attached to medical devices, and further, are effective for inhibiting the formation of glycocalyx by the microorganisms which facilitate their attachment to the medical devices. Additionally, according to the Examiner, Domenico discloses that bismuth ions and salicylate ions, when combined, have an additive effect on inhibiting bacterial growth. The Examiner also alleges that Modak describes treating polymeric medical articles, such as vascular catheters, with chlorhexidine compounds, silver sulfadiazine and benzalkonium chloride, and further, that Darouiche discloses the combination of an antibiotic, such as minocycline, and an antiseptic, such as chlorhexidine, triclosan or silver, for coating catheters. The Examiner contends that it would have been obvious for artisan of ordinary skill to combine the elements of the cited references according to the instantly claimed invention, rendering the claims obvious.

In Applicants' prior response (dated 8/28/08), Applicants submitted that the anti-infective combinations disclosed in the pending claims, for example, the minocycline and chlorhexidine combination, exhibited surprising and unexpected results over the combinations described in the prior art. However, the Examiner has stated that the synergistic effect of the compounds is not

unexpected. Furthermore, the Examiner states that even if the synergy were unexpected, the data relied upon is against specific species of microbes, specific compounds, and specific amounts of components used.

Applicants respectfully traverse the rejection and submit that the present claims are not obvious over the cited art. Evidence of unobvious or unexpected advantageous properties rebuts *prima facie* obviousness, and the presence of a property not possessed by the prior art is sufficient evidence of non-obviousness. *See M.P.E.P. 716.02(a); see also In re Papesch, 315 F.2d 381 (C.C.P.A. 1963).* Applicants maintain that the claimed invention encompasses, *inter alia*, the unexpected discovery that the specifically claimed antiseptic and antibiotic agents of the claimed invention, when combined, exhibit a synergistic increase in their combined antimicrobial efficacy and/or are effective in reducing the development of antibiotic resistant microorganisms, as clearly demonstrated by the Examples.

Applicants respectfully disagree with the Examiner's position that the data relied upon is insufficient to conclude that the results are unexpected and surprising. Applicants submit that the Examples (discussed in detail below) are not only commensurate in scope with the claims, with respect to specific compounds and their claimed amounts, but also support the claimed invention's surprising and unexpected results. The current specification contains 21 Examples, which exemplify various embodiments of the invention. Applicants submit that the Examiner's conclusion of unpersuasive data is misplaced and without merit. The data provided by the Examples in the specification are not subjective measurements of anti-infective or anti-microbial effects. Rather, the data are based on specific and objective comparisons between individually tested compounds and their combinations.

Regarding the presently claimed embodiment of the combination of minocycline and chlorhexidine compounds, Applicants direct the Examiner's attention to Examples 1-4, 8, and 14-21. Each of these Examples describes the effect of the combination of these components in varying amounts within the claimed ranges. Specifically, Example 1 demonstrates the effectiveness of antiseptics against the tested bacterial strains as well as the lesser effectiveness of antibiotics against the tested bacterial strains due to bacterial resistance. Based on this data alone, one skilled in the art would not expect the combination of such compounds to provide any synergistic antimicrobial effect, particularly since the antibiotics were ineffective.

Example 2 then demonstrates the antimicrobial effect of individual antibiotics, individual antiseptics, and specific combinations of antibiotics and antiseptics, including minocycline and chlorhexidine. Furthermore, Example 2 also notes that minocycline is less likely to develop resistant bacteria when used at lower concentrations, and further, at higher bacterial cell densities, minocycline's MIC increased 4-fold. See paragraph [0051]. Again, without the teaching of the instant application, one skilled in art would not necessarily expect to arrive at the results disclosed by the applications.

Contrary to the Examiner's positioning, Examples 4, 8, and 14-21 disclose tests of various concentrations of minocycline and chlorhexidine compounds, including 1%, 3%, and 5% (w/v) for both compounds. The results demonstrate that minocycline in combination with a chlorhexidine compound was a preferred embodiment as it avoided bacterial resistance (see paragraph [0068]). The data also demonstrated broad spectrum antimicrobial activity (see paragraph [0213]); enhanced antimicrobial activity for a longer period of time when compared against other antimicrobial catheters (see paragraph 0222); significantly lower colonization over other catheter groups (see paragraph [0231]); and reduced adherence of a range of different bacterial strains (see paragraphs [0236], [0239], [0248], and [0254]).

Similar results are exemplified for combinations of minocycline, triclosan, and bismuth salt; minocycline, benzalkonium chloride, and bismuth salt; triclosan and bismuth salt; and minocycline and bismuth salt. The data detailing the surprising results of these combinations were explained at length in the previously submitted response (See Amendment filed 8/28/08). To summarize, Example 2 demonstrates a composition comprising both the antiseptic triclosan and the antibiotic minocycline, which exhibited an unexpected increase in antimicrobial effectiveness against *S. epidermidis* cultures that was greater than the additive effect of each agent's independent antimicrobial activity (*i.e.*, a synergistic antimicrobial effect). *See* the specification at pages 13-14. Specifically, a composition comprising both agents could achieve the same antimicrobial effectiveness against the bacterial culture at a lower concentration than the combined amounts of two independent compositions comprising triclosan or minocycline. *See* the specification at page 13, Table III (8.35% of the combined independent effective concentrations of triclosan and minocycline was equally effective against *S. epidermidis* when the agents were used in a single composition.). Additionally, synergistic antimicrobial effects were also observed when minocycline was combined with triclosan and a bismuth salt (*i.e.*,

bismuth nitrate). See the specification at page 24, Table X (A composition comprising bismuth nitrate alone, and a composition comprising triclosan and minocycline both produced no zone of inhibition on a lawn of *P. aeruginosa*. When all three agents were combined in a single composition, a 15 mm zone of inhibition was induced on the lawn.).

Applicants also demonstrated that a similar unexpected synergistic increase in antimicrobial activity was observed when minocycline was combined with other antimicrobial agents of the claimed invention. For example, as shown in the Examples on pages 31-35, a composition comprising minocycline and any one of nine different bismuth salts, for example, bismuth citrate or bismuth salicylate, exhibited a synergistic increase in antimicrobial activity that was greater than the additive effect of the agents' independent activities. See the specification at Tables XV and XVI. Similarly, a composition comprising benzalkonium chloride ("BZK"), minocycline, and bismuth nitrate exhibited a synergistic increase in antimicrobial effectiveness against *S. epidermidis*. As shown in the Example at pages 26-28, a composition formulated with any two of BZK, minocycline, and bismuth nitrate, exhibited an antimicrobial effectiveness similar to a composition comprising only BZK. See the specification at p. 28, Table XIII. However, when all three agents were combined in a single composition, the number of cfu/mm² was reduced to only 2.5, demonstrating a synergistic effect between the three antimicrobial agents.

Applicants submit that the data in the Examples are commensurate with the presently claimed embodiments. As noted in MPEP 716.02(d)(I), "nonobviousness of a broader claimed range can be supported by evidence based on unexpected results from testing a narrower range if one of ordinary skill in the art would be able to determine a trend in the exemplified data which would allow the artisan to reasonably extend the probative value thereof." MPEP 716.02(d) citing *In re Kollman*, 595 F.2d 48, 201 USPQ 193 (CCPA 1979). Applicants submit that the Examples demonstrate such a trend with the various compound concentration ranges tested. Additionally, the Examples test the specifically claimed compounds. Contrary to the Examiner's statements, the Examples contain the exact combinations of compounds as are presently claimed.

Regarding the Examiner's assertion that the claims encompass "any infective agent", we direct the Examiner's attention to the fact that the claims are directed to a product, specifically to an anti-infective medical article comprising specific components in specific ranges. According to MPEP 2111.02(II), "if the body of a claim fully and intrinsically sets forth all of the

limitations of the claimed invention, and the preamble merely states, for example, the purpose or intended use of the invention, rather than any distinct definition of any of the claimed invention's limitations, then the preamble is not considered a limitation and is of no significance to claim construction." MPEP 2111.02 *citing Pitney Bowes, Inc. v. Hewlett-Packard Co.*, 182 F.3d 1298, 1305, 51 USPQ2d 1161, 1165 (Fed. Cir. 1999). The fact that the medical articles have an intended anti-infective effect is not a limitation of the claim, and therefore does not require that Applicants claim every infective agent known in the art. Nonetheless, Applicants have demonstrated an array of bacterial strains that were used to exemplify the effectiveness of the claimed invention throughout the Examples.

As described above, the compounds encompassed by the claims of the instant invention have been shown to exhibit unexpected results with regard to their synergistic antimicrobial activity, and further, their ability to inhibit the development of antibiotic resistance. Such surprising results support the non-obviousness of the present claims over the cited art. Therefore, Applicants respectfully request that the rejection be withdrawn.

III. Double Patenting

Claims 1-4, 7-16, 19-31, 33-37 and 39 stand rejected under the judicially created doctrine of obviousness-type double patenting over claims 1-55 of U.S. Patent No. 6,106,505 ("the '505 patent) and claims 1-15 of U.S. Patent No. 6,582,719 ("the '719 patent") in view of Raad, Domenico, Modak and Darouiche. The Examiner contends that claims 1-55 of the '505 patent are directed to an anti-infective medical article, such as an intravenous catheter, which has been impregnated with chlorhexidine free base and triclosan, and can further comprise silver sulfadiazine. According to the Examiner, in view of Raad, Domenico, Modak and Darouiche, it would have been obvious to modify the medical article of the '505 patent to comprise minocycline and chlorhexidine; minocycline, triclosan and bismuth; or minocycline and bismuth.

With regard to claims 1-15 of the '719 patent, the Examiner alleges that the claims of the '719 patent encompass a medical article impregnated with the antibiotics and antiseptics of the instant claims except for the agents bismuth citrate, bismuth salicylate, chlorhexidine gluconate and zinc salt. According to the Examiner, in view of Raad, Domenico and Modak, it would have been obvious for a skilled artisan to modify the medical article of the '719 patent to include such agents.

Without conceding to the Examiner's contentions, Applicants respectfully submit that the appropriate action will be taken (*e.g.*, through the submission of a Terminal Disclaimer), as the Examiner indicates allowable subject matter in the instant application.

IV. Conclusion

In view of the above amendments and remarks, it is respectfully requested that the application be reconsidered and that all pending claims be allowed and the case passed to issue. If there are any other issues remaining which the Examiner believes could be resolved through either a Supplemental Response or an Examiner's Amendment, the Examiner is respectfully requested to contact the undersigned at the telephone number indicated below. Applicants believe that no fees are due. If, however additional fees are due, the Commissioner is hereby authorized to charge payment of fees or to credit any overpayment associated with this communication to Deposit Account No. 02-4377.

Respectfully submitted,

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